Tetrahedron Letters,Vol.26,No.13,pp 1611-1614,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

A RELAY APPROACH TO (+)-PLEUROMUTILIN. III. DIRECT DEGRADATION OF THE NATURAL PRODUCT TO THE KEY DIKETONE INTERMEDIATE AND ITS CHEMOSPECIFIC FUNCTIONALIZATION[1]

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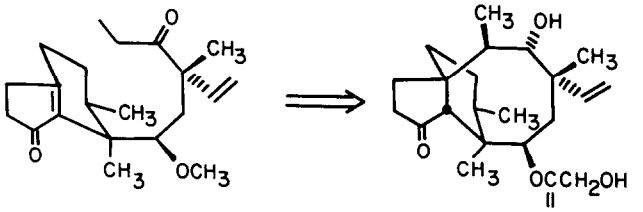
Summary: Pleuromutilin or tiamulin can be degraded to the important bicyclic relay compound (-)-1 in only four steps. Various methods for achieving chemoselective functionalization of 1 are set in focus.

In the preceding Letter,[1] we describe a reaction sequence that proceeds with complete retention of chirality to provide levorotatory diketone 1, a molecule envisioned as a key intermediate in a projected total synthesis of (+)-pleuromutilin (2). Herein we report on the feasilbility of degrading (+)-2 or tiamulin to (-)-1 in only four steps (67% overall yield) and detail relevant transformations of this (now) conveniently available relay substance.

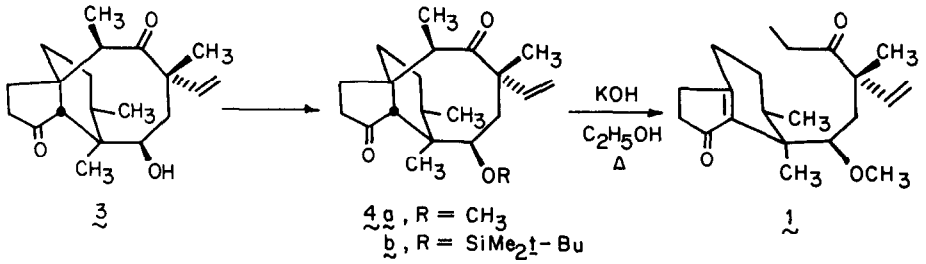


(-)-1 2

The initial transformation involves pyridinium chlorochloromate oxidation of the secondary hydroxyl group in either antibiotic. When methanol is utilized as solvent for the subsequent alkaline hydrolysis (5% KOH), only ester saponification is observed.[3] The nonoperation of retro-Michael fragmentation is the likely result of the lowered reaction temperature. These conditions afford 3 in 79% overall yield (Scheme I). Prolonged treatment (2 days) of 3 with methyl triflate and 2,6-di-tert-butylpyridine in dichloromethane

solution at room temperature[4] led chemospecifically to **4**[5] (100%). At this point, the aforementioned ability of such 1,5-diketones to undergo base-promoted bond scission was im-

SCHEME I



3

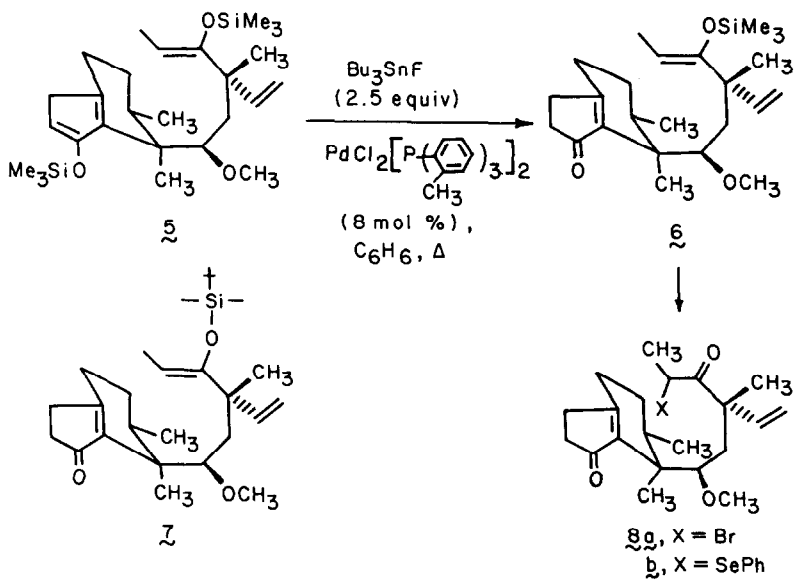
4a, R = CH_3
b, R = $SiMe_2$t-Bu

1

plemented. Thus heating **4a** in ethanolic potassium hydroxide solution provided **1** (85%). This material was shown by 300 MHz ^1H NMR, IR, and $[\alpha]_D^{20}$ to be identical to the sample obtained earlier.[1]

The next goal was to distinguish suitably between the pair of ketone functionalities in **1** as a prelude to achieving cyclization. One successful protocol involved conversion to **5**, followed by selective desilylation of the dienol ether subunit. The procedure of Kuwajima

SCHEME II



5

6

7

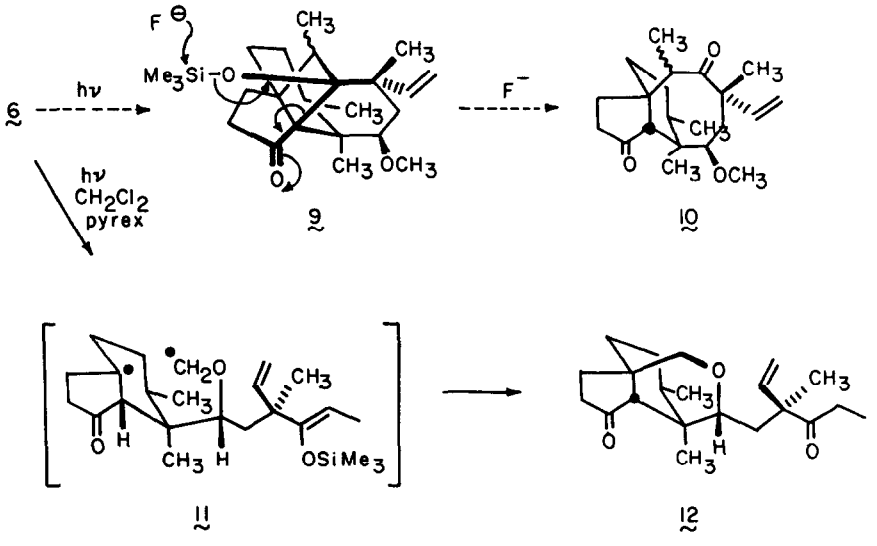
8a, X = Br
b, X = SePh

and Urabe[6] worked splendidly to furnish **6**, $[\alpha]_D^{20}$ -34.9° (CCl_4), in 84% overall yield as a single stereoisomer. Because kinetically controlled conditions were utilized to set the stereostructure of the enolate in the sidechain, we are prompted to formulate **6** as the (Z)-isomer.[7] tert-Butyldimethylsilyl triflate offers somewhat greater chemoselectivity in this system and allows (LDA, HMPA, THF, -78° → 25 °C)[8] for the direct conversion of **1** to **7** (50%), $[\alpha]_D^{25}$ -21.5° (CCl_4).

With the acquisition of these substrates, methods were applied to introduce more varied substituents in regiocontrolled fashion. For example, exposure of **6** to N-bromosuccinimide (THF, 0°C)[9] and phenylselenenyl chloride (C_6H_6, 20°C)[10] gave rise to **8a** (86%) and **8b** (69%), respectively, as mixtures of inseparable diastereomers.

Although the stage has now been set to examine a variety of cyclization schemes, we became most enamoured with the possibility of coaxing **6** into [2+2] photocycloaddition. The significant issue of ring size is reduced to creating a fused [6,4] carbocyclic substructure as seen in **9** (Scheme III). Furthermore, should **9** be obtained, its exposure to fluoride ion would be expected to induce fragmentation and deliver **10** having the pleuromutilin framework. Of the several conditions examined for photoactivation of **6**, those developed by Cargill[11] proved most efficacious. Irradiation of dilute CH_2Cl_2 solutions with a 450 W Hanovia lamp through pyrex for 4-6 h resulted in formation of a single photoisomer (53%). However, instead of intramolecular photocycloaddition, hydrogen atom abstraction from the methoxyl

SCHEME III



group by the α-cyclopentenone carbon is strongly favored.[12] Collapse of the presumptive biradical so produced (**11**) delivers **12**, a colorless oil exhibiting $[\alpha]^{25}$ +67.0° ($CHCl_3$). Qualitatively, therefore, the methoxyl protecting group is unsuited to this purpose. The same detractive structural feature is absent in **4b**, which is directly prepared from **3** and is capable of conversion to the silylated counterpart of **1** (95%). The photochemistry of this compound is currently under investigation.

In summary, an array of intermediates potentially convertible to pleuromutilin are shown to be readily available. To reach the intended goal, it is necessary to achieve construction of the cyclooctyl ring. Studies bearing on this chemistry will be described in due course.

Acknowledgments: This research was supported by grants from the National Institutes of Health (GM 30827) and the Eli Lilly Company. In addition, we thank Dr. Russ Buchman (SDS Biotech) for providing a generous quantity of tiamulin.

References and Notes

1. Part I: Paquette, L. A.; Wiedeman, P. E. preceding paper. Part II: Paquette, L. A.; Bulman-Page, P.C. preceding paper.
2. (a) National Science Foundation Predoctoral Fellow, 1981-1984. (b) NATO Postdoctoral Fellow of the Science and Engineering Research Council, 1981-1983.
3. Naegeli, P. Ph.D. Thesis ETH, Zurich, 1961.
4. Arnarp, J.; Lönngren, J. Acta Chem. Scand. **1978**, B32, 465.
5. All new compounds described herein gave correct elemental analysis and/or accurate mass spectral data. All ^1H NMR, ^{13}C NMR, and IR spectra are also in accord with the assigned structures.
6. (a) Kuwajima, I.; Urabe, J. J. Am. Chem. Soc. **1982**, 104, 6831. (b) Urabe, H.; Takano, Y.; Kuwajima, I. Ibid. **198**, 105, 5703.
7. (a) Heathcock, C. H.; Buse, C. T.; Klaschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. J. Org. Chem. **1980**, 45, 1066. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. J. Am. Chem. Soc. **1976**, 98, 2868. (c) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. J. Org. Chem. **1980**, 45, 48.
8. Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. Tetrahedron Lett. **1981**, 3455.
9. (a) Reuss, R. H.; Hassner, A. J. Org. Chem. **1974**, 39, 1785. (b) Blanco, L.; Amice, P.; Conia, J. M. Synthesis **1976**, 194
10. Danishefsky, S.; Yan, C. F. Synth. Commun. **1978**, 8, 211.
11. Cargill, R. L.; Dalton, J. R.; Morton, G. H.; Caldwell, W. E. Org. Synth. **1984**, 62, 118.
12. Such excited state behavior is precedented: Ariel, S.; Askari, S.; Scheffer, J. R.; Trotter, J.; Walsh, L. J. Am. Chem. Soc. **1984**, 106, 5726 and relevant references cited therein.

(Received in USA 19 November 1984)